

# ACOG

Committee on  
Genetics

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# Committee Opinion



Number 318, October 2005

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## Screening for Tay–Sachs Disease

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Screening for Tay–Sachs disease.  
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2005;106:893–4.

**ABSTRACT:** *Tay–Sachs disease (TSD) is a severe progressive neurologic disease that causes death in early childhood. Carrier screening should be offered before pregnancy to individuals and couples at high risk, including those of Ashkenazi Jewish, French–Canadian, or Cajun descent and those with a family history consistent with TSD. If both partners are determined to be carriers of TSD, genetic counseling and prenatal diagnosis should be offered.*

Tay–Sachs disease (TSD) is a lysosomal storage disease in which GM<sub>2</sub> gangliosides accumulate throughout the body. The accumulation of these gangliosides in the central nervous system results in a severe progressive neurologic disease that causes death in early childhood.

The TSD carrier rate in Jewish individuals of Eastern European descent (Ashkenazi) is approximately 1 in 30; the carrier rate for non-Jewish individuals is estimated to be 1 in 300. It has been determined that individuals of French–Canadian and Cajun descent also have a greater carrier frequency than the general population.

The enzyme hexosaminidase occurs in two principal forms, Hexosaminidase A and Hexosaminidase B. Hexosaminidase A is composed of one  $\alpha$  subunit and one  $\beta$  subunit, whereas Hexosaminidase B is composed of two  $\beta$  subunits. Tay–Sachs disease is caused by a deficiency of Hexosaminidase A, whereas Sandhoff disease is caused by a deficiency of both Hexosaminidase A and Hexosaminidase B. Both of these diseases are transmitted in an autosomal recessive fashion. Laboratories report Hexosaminidase A levels as a percentage of total hexosaminidase activity. Hexosaminidase A is almost completely absent in patients with classical TSD. The percentage of Hexosaminidase A activity in carriers usually is less than 55% of total activity, whereas Hexosaminidase A activity in noncarriers generally is more than 60% of total activity. Tay–Sachs disease can be diagnosed prenatally by measuring hexosaminidase activity in samples obtained by amniocentesis or by chorionic villus sampling.

Carrier screening can be performed by molecular analysis, biochemical analysis, or both. Molecular analyses of the  $\alpha$  subunit gene for TSD have been reported in both Jewish and non-Jewish populations. Molecular analysis of three mutations will detect 94% of carriers in the Ashkenazi Jewish population, compared with biochemical analysis, which will detect 98% of carriers.

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Different mutations have been found in other ethnic groups. Biochemical analysis should be used in low-risk populations because molecular analysis detects less than 50% of carriers in these populations.

Test results of biochemical carrier screening using serum are inaccurate when performed in women who are pregnant or taking oral contraceptives. If the serum test is used for pregnant women, many of them will be misclassified as carriers. If biochemical testing is to be done in women who are pregnant or taking oral contraceptives, leukocyte testing must be used. If both partners are determined to be carriers of TSD, genetic counseling and prenatal diagnosis should be offered.

When the serum test result is inconclusive, biochemical analysis should be performed on leukocytes from peripheral blood. DNA analysis may be helpful for those individuals whose leukocyte test results are inconclusive and those individuals whose test results are positive to rule out a rare pseudodeficiency condition.

Pseudodeficiency refers to a state in which asymptomatic individuals have a low amount of Hexosaminidase A activity when tested with conventional artificial substrate. However, these normal individuals without Hexosaminidase A are able to catalyze the breakdown of natural substrate GM<sub>2</sub> ganglioside. Pseudodeficiency mutations comprise approximately one third of the mutations identified in non-Jewish individuals. Because some of these individuals are compound heterozygotes for a Tay-Sachs mutation and a pseudodeficiency allele, the delineation of their precise genotype for reproductive purposes usually requires further biochemical assessment complemented with DNA analysis.

Based on the preceding information, the Committee on Genetics makes the following recommendations:

1. Screening for TSD should be offered before pregnancy if both members of a couple are of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with TSD also should be offered screening.
2. When one member of a couple is at high risk (ie, of Ashkenazi Jewish, French-Canadian, or Cajun descent or has a family history consistent with TSD) but the other partner is not, the high-risk partner should be offered screening. This is particularly important if there is uncertainty

about ancestry or if there is a family history consistent with TSD. If the high-risk partner is determined to be a carrier, the other partner also should be offered screening. If the woman is already pregnant, it may be necessary to offer screening to both partners simultaneously to ensure that results are obtained promptly and that all options are available to the couple.

3. Biochemical analysis should be used for individuals in low-risk populations.
4. If TSD biochemical screening is performed in women who are pregnant or taking oral contraceptives, leukocyte testing must be used.
5. Ambiguous screening test results or positive screening test results in individuals should be confirmed by biochemical and DNA analysis for the most common mutations. This will detect patients who carry genes associated with mild disease or pseudodeficiency states. Referral to a specialist in genetics may be helpful in these cases.
6. If both partners are determined to be carriers of TSD, genetic counseling and prenatal diagnosis should be offered.

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